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EVALUATING PHARMACOKINETICS AND PHARMACODYNAMICS OF INTRAVENOUS BUSULFAN IN PEDIATRIC PATIENTS RECEIVING BONE MARROW TRANSPLANTATION

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Background: Busulfan (BU) is a commonly used conditioning agent in bone marrow transplant (BMT). However, it is a narrow therapeutic index drug which has a strong correlation between area-under-curve (AUC) and both efficacy and toxicity. Studies in pediatric patients have suggested that children less than 4 years of age have a greater clearance and thus lower AUC at standard adult doses. The goal of this retrospective analysis was to evaluate any age-related pharmacokinetic and pharmacodynamic differences in pediatric patients who received BU as a conditioning agent. **Methods:** From 2001 to 2006, 21/77 pediatric patients who received BMT were reviewed. There were 15 males and 6 females with a mean age of 6 years. Diagnoses of leukemia (n = 11), HL (n = 3), MDS (n = 2), and other (n = 5) were included. 16 patients received BU + cyclophosphamide (CY) while 5 patients received BU + another agent. There were 20 allogeneic and 1 autologous transplants among which 16 were HLA matched and 5 were mismatched. **Results:** Average BU clearance in patients younger than 4 years old (n = 8) was 4.1 ± 1.0 (ml/min)/kg vs. 3.1 ± 0.7 (ml/min)/kg in patients older than 4 years old (n = 13) (p = 0.02). The corresponding averages for AUC were 998 ± 226 μM•min vs.1155 ± 183 μM•min (p = 0.12). No patients younger than 4 years old developed veno-occlusive disease (VOD) while 5 of the older patients did (p = 0.044). There were no significant differences in terms of engraftment, graft-vs-host and relapse. **Conclusion:** There were significant age-related pharmacokinetic differences in pediatric patients less than 4 years of age receiving BU for conditioning prior to BMT. There was a decrease in drug toxicity seen in these patients. Patients younger than 4 years old might not need routine pharmacokinetic monitoring.

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CEREBRAL TOXOPLASMOSIS FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) FOR MALIGNANT LYMPHOMA: MISINTERPRETATION AS RELAPSED LYMPHOMA ON INITIAL MRI STUDIES

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Introduction: Infections are a major cause of death in allogeneic hematopoietic stem cell transplant recipients. Cerebral toxoplasmosis is a life-threatening, but fortunately rare protozoal infection even in this high risk population. Establishment of the correct diagnosis may be hindered by non-specific clinical symptoms and uncharacteristic findings in imaging studies. Here, we report the case of a 15-year-old boy with disseminated anaplastic large cell lymphoma (ALCL) and post –transplant cerebral toxoplasmosis misinterpreted as relapsed lymphoma on initial MRI. **Case Report:** The 15-year old boy received an allogeneic HSCT from a matched unrelated donor for treatment of refractory ALCL. Central nervous system involvement was excluded by normal MRI studies and the absence of lymphoma cells in cerebrospinal fluid (CSF). Complications until day +100 included acute GvHD, grade II, viral reactivations (polyomavirus, CMV and EBV) and a delayed immune system recovery. Four months post-transplant, he presented with severe headaches, fever and nausea. A cranial CT scan revealed multiple hypodense areas in both hemispheres without hemorrhage or evidence of elevated intracranial pressure. Subsequent MR imaging studies were interpreted as intracerebral relapse of lymphoma. The patient became somnolent, developed seizures and was admitted to the ICU. A diagnostic work-up was initiated including blood and CSF cultures, PCR-testing for pathogens in blood and CSF, a bone marrow aspirate and brain biopsy. Still unaware of the results, the patient was treated with broad-spectrum antibacterial drugs, acyclovir, ambisome, rituximab, dexamethasone and pyrimethamine/sulfadiazine. His condition improved rapidly; cerebral toxoplasmosis was proven by evidence of a positive PCR in CSF and detection of the pathogen in brain tissue. Another MRI two weeks later showed the characteristic findings of cerebral toxoplasmosis with numerous ring-like contrast-enhancing lesions in both hemispheres. One year later, the patient still has residual MRI findings, but without neurological abnormalities. He is kept on toxoplasmosis maintenance therapy. **Conclusion:** In hematopoietic stem cell transplant recipients, a diagnosis of cerebral toxoplasmosis should be considered in every patient with sudden onset of acute, neurological symptoms regardless of the presence of characteristic findings on initial imaging studies.

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LONG TERM FOLLOW-UP IN THREE PEDIATRIC PATIENTS WITH FARBER DISEASE, TYPE 2/3, FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM RELATED AND UNRELATED DONORS

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Introduction: Farber Disease (FD) is an autosomal-recessively inherited, lysosomal storage disorder caused by acid ceramidase deficiency. FD, type 2/3, patients lack central nervous system involvement, their clinical phenotype is dominated by the triad of a hoarse voice, subcutaneous nodules and inflammatory granuloma around the joints, resulting in severe, progressive contractures, deviation of joints and finally considerable impairment of activities of daily living or even complete immobility. Respiratory tract involvement leads to death in the third or fourth decade of life. Allogeneic hematopoietic stem cell transplantation (HSCT) has been described as a curative option for these patients. Here, we present the long term follow-up data of three children after allogeneic HSCT with encouraging results. **Patients and Methods:** The three children were transplanted between May 2001 and February 2004 at the age of 2, 3 and 4 years, respectively. The patients (female 2, male 1) received an allogeneic HSCT (MRD 2, MUD 1; stem cell source: BM 2, PBSC 1) after busulfan-based myeloablative conditioning regimens. GvHD prophylaxis consisted of CsA and short course MTX with (MUD) or without (MRD) rabbit-ATG. Transplant-related toxicities included acute GvHD, grade II (3), CMV-reactivation (1), bacterial infections (1) and CsA-associated neurotoxicity (2). No chronic GvHD has been observed. Donor cell chimerism is complete in one patient and partial in two patients. The follow-up period is in a range between three and six years. Following the first year post-transplant, all children were seen at least twice yearly by the outpatient pediatric BMT unit and once yearly by pediatric rheumatology. Pre-transplant all children had severe joint involvement with pain and considerable restriction of motility; post-transplant a rapid improvement and finally resolution of all nodules and granulomas could be observed without evidence of residual impaired function. The children's mental and motor development is normal. Routine laboratory and organ function tests, endocrinological and neurological studies have yielded normal results. The more severely affected child with CsA-associated neurotoxicity (stroke like event with seizures) has recovered completely. **Summary:** Follow-up evaluation in three children three to six years after allogeneic HSCT for Farber Disease, type 2/3, has revealed encouraging long-term results without evidence of relapse, chronic GvHD or late effects.

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BUSULFAN AND SINGLE-DOSE MELPHALAN AS PREPARATIVE THERAPY FOR INFANTS AND YOUNG CHILDREN UNDERGOING STEM CELL TRANSPLANTATION FOR LEUKEMIA: A SINGLE CENTER EXPERIENCE

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Between January, 1996 and October, 2006, we treated 29 patients under the age of 4 with ALL (n = 15), AML (n = 11), JMML (n = 2), and CML (n = 1) with a preparative regimen of Busulfan, 37.5 mg/m^2 p.o. q 6 hours for 16 doses and Melphalan 140 to 180 mg/

m^2. Patients undergoing unrelated donor transplants received antithymocyte globulin, 30 mg/kg, on days -2, -1, and +6. The last 8 Busulfan doses were adjusted to achieve areas under the concentration × time curve of 600 – 900 micromol.min/liter. Family donor transplant recipients (n = 9), received Cyclosporine/Methotrexate/Leukovorin as GVHD prophylaxis; unrelated donor transplant recipients (n = 19) received Cyclosporine/Steroid prophylaxis; one patient underwent syngeneic BMT. With a minimum of 12 months and a median of 66 months follow-up, 19 of the 29 (66%) survive event-free and 22 of the 29 (76%) survive overall. Five patients relapsed. Three patients in relapse at the time of BMT achieved CR but relapsed at 5, 5 and 6 months. Two patients with Ph+ ALL relapsed 15 and 26 months after BMT and survive event-free 42+ and 39+ months, respectively, after 2nd transplants with TBI-containing regimens. One patient with AML in CR2 suffered rejection of an unrelated cord blood but survives event-free 63+ months after autologous stem cell infusion. Four died of transplant-related complications (multi-organ failure, disseminated adenovirus infection, enterococcal sepsis, and hemolytic-uremic syndrome with Aspergillosis). Toxicity was considerable and included mucositis requiring parental nutrition (29 of 29), hemolytic uremic syndrome (n = 5), pulmonary hemorrhage (n = 3), veno-occlusive disease (n = 3), seizures (n = 1).

Our data suggest that although this is a moderately toxic regimen, Busulfan/Melphalan shows promising activity as preparative therapy for infants and very young children with leukemias, avoids total body irradiation, and produces outcomes similar to those previously reported for patients in this age group.

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UNRELATED DONOR CORD BLOOD STEM CELL TRANSPLANTATION FOR LEUKOCYTE ADHESION DEFICIENCY (LAD)

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Leukocyte adhesion deficiency (LAD) is a rare disorder characterized by the congenital absence of CD18 resulting in the loss of expression of leukocyte CD11/CD18 integrins on myeloid cells with resultant life threatening infections. Hematopoietic stem cell transplantation currently provides the only available cure for this disorder. Although there have been reports of some success in transplantation using related family member donors or unrelated marrow donors with either myeloablative or non-myeloablative prepartative regimens, there is little experience with the use of umbilical cord SCT. We present here the first report of a patient transplanted with unrelated donor cord blood (UCB) for severe LAD type 1. The patient was diagnosed at 2 months of age when he presented with failure to thrive, fever, mastoiditis, and lethargy. Laboratory evaluation revealed a WBC of 165,000 (predominantly neutrophils) and flow cytometry documented the absence of neutrophil expression of CD11b and CD18. He was treated with antibiotics and surgical drainage of his mastoid bone. Since no family donors were identified, and given the need to proceed with transplant expeditiously and to minimize the risk of GVHD, unrelated donor cord blood transplant was pursued using a non-myeloablative preparative regimen. A large (16.5×10^7 TNC/kg and 9.5×10^5 CD34 cell/kg) 10 of 10 antigen matched unrelated donor cord blood unit was identified. The preparative regimen included Campath-1H3 (10 mg/d iv days -21 to – 19), fludarabine (30 mg/m^2/d iv days -8 to -4) and melphalan (140 mg/m^2 iv day -3). GVHD prophylaxis consisted of CSA + mycophenolate. He engrafted and was transfusion independent by day 16. He had no evidence of GVHD, and donor-host studies revealed 40% donor on day 15. His donor chimerism fell to 16% by STR on day 41 confirmed 100% recipient by VNTR. His cyclosporine was discontinued and an extensive viral screen showed no evidence of CMV, EBV, HHV6, adenovirus, or Hepatitis B. Over the next several months, his donor chimerism slowly rose to 48% where it has remained stable for the past 7 months with 44% of his granulocytes positive for CD11b/CD18. He remains clinically well off all immune suppression 13 months post-transplant with normal growth and development.

Conclusion: UCB is a viable source of stem cells for LAD patients.

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DURATION OF HOSPITALIZATION IN THE FIRST 100 DAYS FOLLOWING REDUCED INTENSITY CONDITIONING FOR NON-MALIGNANT DISORDER TRANSPLANTS IN CHILDREN

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Background and Objective: A novel reduced intensity conditioning (RIC) regimen was used for hematopoietic stem cell transplantation (HSCT) in childhood non-malignant disorders in an effort to reduce regimen related organ toxicities and the incidence and severity of graft-versus-host disease (GVHD). Recipient immunosuppression was used to achieve donor cell engraftment and post-transplant monitoring included infection surveillance until immune reconstitution. This retrospective study evaluates duration of hospitalization within the first 100 days following HSCT in RIC recipients. **Methods:** Thirty patients (7 months to 17 years) with hemoglobinopathies (4), bone marrow failure (7), immune dysfunction (11), metabolic disorders (7), and mitochondrial myopathy (1) underwent HSCT following conditioning with alemtuzumab (48 mg; day -21 to -19), fludarabine (150 mg/m^2; day -8 to -4), and melphalan (140 mg/m^2 [24] or 70 mg/m^2 [6] on day -3). Doses were lower for patients <10 kg. Stem cell sources included peripheral blood (PBSC) (4), cord cells (UCB) (5), and bone marrow (BM) (21). Seven patients (5 UCB; 2 BM/PBSC) received 1–2 antigen mismatched products. GVHD prophylaxis included a calcineurin inhibitor, methotrexate (except in 4 UCB transplants) and methyl prednisolone. **Results:** Durations of hospitalization in the first 100 days is shown in Table 1; all had donor cell engraftment. Median number of in-patient days was 22.5 for the group and was similar for unrelated and related HSCT (Table 1). UCB recipients stayed longer. Eight patients were hospitalized for >30 days (3 unrelated and 1 related BM, 4 mismatched UCB) for hemolysis (1), organ failure (3), GVHD (3) and infection. Infections which required hospitalization included bacteria (6), non-CMV viruses (3), CMV reactivation (3), CMV disease (2), and C. difficile (4). Three patients died before day 100 of GVHD (1), progressive disease (1), and infection (1). **Conclusions:** Recipients of this RIC regimen had an acceptable duration of hospitalization in the first 100 days post-transplant. Infectious complications and GVHD accounted for prolonged hospitalization (>30 days) in the majority of patients.

Table 1. *In-patient stay in the first 100 days following HSCT*

Recipient Details (number)	Median days of hospitalization (range)	Mean days of hospitalization
Total (30)	22.5 (12–88)	29.5
Alive beyond 100 days (27)	22 (12–84)	27
Died prior to day 100 (3)	51 (18–88)	51.7
UCB (all unrelated, mismatched) (5)	46 (21–88)	50.3
BM + PBSC recipients (25)	21.5 (12–84)	26.3
Unrelated BM or PBSC (HLA-matched) (11)	27 (14–84)	32.1
Unrelated BM or PBSC (mismatched) (2)	20 (15–25)	20
Matched related donors (12)	21 (12–42)	21.8